

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference <b>X16067</b>	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. <b>PCT/US2004/009272</b>	International filing date ( <i>day/month/year</i> ) <b>08 April 2004 (08.04.2004)</b>	Priority date ( <i>day/month/year</i> ) <b>21 April 2003 (21.04.2003)</b>
International Patent Classification (IPC) or national classification and IPC <b><sup>7</sup> C07D 495/04, 493/04, 311/94, A61K 31/352, A61P 35/00</b>		
Applicant <b>ELI LILLY AND COMPANY</b>		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
  2. This REPORT consists of a total of 9 sheets, including this cover sheet.
- In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input checked="" type="checkbox"/> | Box No. II   | Priority  |
| <input checked="" type="checkbox"/> | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input type="checkbox"/>            | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. +41 22 740 14 35	Date of issuance of this report <b>21 October 2005 (21.10.2005)</b>  Authorized officer  <div style="text-align: center; font-weight: bold; font-size: 1.2em;">Ellen Moyse</div>  Telephone No. +41 22 338 89 75
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

4/11

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		<b>FOR FURTHER ACTION</b> See paragraph 2 below	
International application No. PCT/US2004/009272	International filing date (day/month/year) 08.04.2004	Priority date (day/month/year) 21.04.2003	
International Patent Classification (IPC) or both national classification and IPC C07D495/04, C07D493/04, C07D311/04, A61K31/352, A61P35/00			
Applicant ELI LILLY AND COMPANY			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application



2. **FURTHER ACTION**

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

<p>Name and mailing address of the ISA:</p> <div style="text-align: center;">  </div> <p>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</p>	<p>Authorized Officer</p> <p style="text-align: center;">Stroeter, T</p> <p>Telephone No. +49 89 2399-8088</p> <div style="text-align: right;">  </div>
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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/009272

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/009272

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**Box No. II    Priority**

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1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/009272

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 39-43

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 39-43
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/009272

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
Industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-44
	No: Claims	
Inventive step (IS)	Yes: Claims	1-44
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-38, 44
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

**see form 210**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 39-43 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1    Subject-matter of the independent claims**

The present application is directed to benzopyranes which are further annellated (independent claims 1 and 31) and pharmaceutical compositions containing such compounds (independent claim 38). These compounds are estrogen receptor-beta agonists and as such are useful in the treatment of diseases such as cancer or benign prostatic hyperplasia (independent claims 39-42 and 44).

**2    Prior art documents**

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 01/64665 A (AKZO NOBEL NV) 7 September 2001

D2: ANDERSON W K ET AL: "Synthesis of 6,9-bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 42, no. 6, 1977, pages 1045-1050, XP002230194 ISSN: 0022-3263

D3: OUDE-ALINK B A M ET AL: "Photolysis of 2-keto-2,3-dihydrobenzofurans, o-hydroxystyrenes and 1-o-hydroxyphenyl-1,5-hexadienes" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 38, no. 11, 1973, pages 1993-2001, XP002230195 ISSN: 0022-3263

D4: WO 03/044006 A (ELI LILLY CO) 30 May 2003

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/009272

D5: US-B-6 630 5081 (DODGE JEFFREY ALAN ET AL) 7 October 2003  
Concerning documents D4 and D5 please see item VI.

**3 Novelty (Article 33(2) PCT)**

The structurally closest prior art compounds can be found in D2 and D3 which differ through present group G which in D2, D3 is CH<sub>2</sub> whereas in the present case it is e.g. O, S, subst. CH, etc. The compounds of D1 are structurally more remote. Present claims 1-44 are therefore novel.

**4 Inventive step (Article 33(3) PCT)**

Document D1 represents the closest prior art since it is the only document revealing estrogen receptor-beta agonists which are structurally related to the presently claimed compounds. In view of this relevant prior art the present problem is the provision of further benzopyrane compounds for use in estrogen receptor-beta mediated diseases. Starting from the known compounds of D1 the skilled man would not have expected that the present modified benzopyrane compounds now having a cycloalkane annellated to the pyrane moiety would also have the same pharmacological activity and therefore their provision is not considered to be obvious when wanting to solve the present technical problem. Present claims 1-44 are therefore inventive.

**5 Industrial applicability (Article 33(4) PCT)**

The subject-matter of the present claims 1-38 and 44 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claims 39-43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VI**



**Certain documents cited**

The International Search Report mentions P-documents D4 and D5 which do not form part of the state of the art according to Rule 64.1(b) PCT. For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid. The Applicant is informed, that these documents reveal estrogen receptor-beta agonists which are structurally close and which might have relevance for the question of inventiveness.

**Re Item VII**

**Certain defects in the international application**

- (1) The requirements of Rule 5.1(a)(ii) PCT are not met since the relevant background art (document D1) has not been identified in the description.
- (2) When entering the regional phase at the EPO, the Applicant is informed that an application may contain more than one independent claim in a particular category only certain circumstances. In the present case it appears that present claims 2 and 3 are in fact dependent (on claim 1), as well as claim 32 (on 31).

**Re Item VIII**

**Certain observations on the international application**

Present claims 24 and 25 lack clarity (Art. 6 PCT) since they are said to be dependent on claim 1, but show fragments corresponding to moiety "G" which are  $C=CF_2$  and  $C=CH_2$ . These meanings are not mentioned in present claim 1.